REMARKS

The Claims

Claims 61-67 and 69-76 are currently pending in the application and are directed to a method of treating bone loss in a mammal or a method of reducing osteoclast activity in a mammal comprising administering an expression vector comprising a nucleic acid encoding osteoprotegerin.

Rejection under 35 U.S.C., first paragraph

Claims 61-67 and 69-76 are rejected under 35 U.S.C., first paragraph, as the specification allegedly does not enable the full scope of the claims. Applicants disagree.

Applicants have provided as evidence of enablement a Declaration of Dr. Jackie Z. Sheng attached as Exhibit B to the response of September 28, 2001, and a publication of Bolon et al. (Molecular Therapy 3, 197-205 (2001)) attached as Exhibit C to the response of September 28, 2001. The Sheng Declaration and Bolon publication clearly show that introduction of a nucleic acid comprising osteoprotegerin into an ovarectomized mouse which is experiencing bone loss gives expression of osteoprotegerein, reduction of osteoclastogenesis in the ovarectomized mouse, and an inhibition of bone resorption. As was previously pointed out, the ovarectomized mouse is a clinically relevant model for loss of bone mass and the results obtained in such a model indicate that introduction of a nucleic acid comprising osteoprotegerin into a human would also reduce osteoclastogenesis and inhibit bone resorption.

The Examiner acknowledges that the Sheng Declaration and the Bolon publication provide "certain evidence" regarding the claimed subject matter, but argues that the evidence only relates to adenoviral vectors comprising OPG delivered to mice by tail injection and that only an OPG-Fc fusion protein achieved sustained circulation in the mice. On this basis, the Examiner argues that evidence fails to support enablement of the claimed

invention with respect to different gene therapy vectors, different routes of administration, and different OPG molecules.

The Examiner also argues that the specification is "silent" as to the claimed subject matter and therefore the Sheng Declaration and the Bolon publication cannot provide support for what is allegedly missing in the specification.

The specification itself describes and enables the claimed invention.

At p. 20, lines 22-24, the specification states that the nucleic acids of the invention are useful for modulating the levels of OPG by anti-sense therapy or gene therapy. It is also stated at p. 33, lines 20-27 that nucleic acid compositions will be suitable for the delivery of part or all of the OPG coding region to cells and tissues as part of an anti-sense or gene therapy regimen. The activity of OPG in reducing osteoclastogeneis and inhbiting bone resorption is extensively disclosed in the application. It is clear that the specification discloses the claimed subject matter. Moreover, as stated in *Genentech v. Novo Nordisk* 42 USPQ2d 1005 (Fed. Cir. 1997) cited by the Examiner, the specification "must supply the novel aspects of an invention in order to constitute adequate enablement". Applicants have clearly supplied the novel aspects, namely the identification and characterization of OPG and its biological activity. Vectors and procedures useful for gene therapy were widely available in the art as evidenced by the many references cited by the Examiner.

The scope of the claimed subject matter does not require undue experimentation.

The Examiner argues that the rapid decline of OPG in serum when administered as part of the Ad-hOPG or Ad-mOPG vectors (as reported in the Bolon publication) is evidence that administering OPG could not achieve a therapeutic effect for treating bone loss. There is no basis for this conclusion. OPG is still present in animals receiving a single dose of Ad-hOPG

and Ad-mOPG even after 25 days (see Figure 1 on p. 199 of Bolon et al.). Routine changes such as increasing amounts of vector that are administered or using more frequent administration could increase serum OPG levels even further and give therapeutic effect. Such changes would not require undue experimentation.

The Examiner further argues that Applicants have not taught how to use vectors other than the adenoviral vector used in the Sheng declaration and the Bolon publication. Citing the Robbins and Orkin references, the Examiner argues that various technical problems have been encountered with gene therapy vectors such as retroviral, herpesvirus, poxvirus, and AAV vectors as well as naked DNA which could make them unacceptable for use in gene therapy. However, the assertion that other gene therapy vectors have not been shown to be therapeutically useful in certain circumstances is not germane to enablement of the present invention. The Examiner has not pointed to any evidence that would suggest that these vectors would not be useful in expressing OPG and reducing bone loss. Moreover, it is clear that given the level of skill in the art and the availability of vectors and procedures for gene therapy as evidenced by the numerous publication in the area, undue experimentation would not be required to test a variety of vectors and procedures for introduction of nucleic acid sequences comprising OPG into mammals for the treatment of bone loss.

The Examiner alleges that the statement on p. 204 of Bolon et al. that "[s]tudies using a more suitable vector are under way to achieve a more realistic, improved gene therapy approach" is an admission that the claimed method is not enabled. The disclosure of Bolon et al. clearly sets forth a working example of the claimed invention. The initiation of additional studies by the authors for the purpose of making improvements on their methods is in no way prejudicial to the results they have already obtained. The purpose of these studies is simply to improve on already working processes.

Claims 61-67 and 69-76 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. It is argued that Claims 61 and 69 are incomplete because there is no step or recitation which relates to the preamble.

Without acquiescing to the rejection and solely to advance prosecution, Applicants have amended Claims 61 and 69 to more distinctly claim the invention. Entry of the amendment is requested.

Claims 61, 65-67, 69 and 73-76 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 2, 11 and 12 of U.S. Patent No. 6,284,740 (hereafter the "'740 patent"). It is argued that the claimed methods in the '740 patent and the present application are obvious variants.

Applicants request that the rejection be held in abeyance pending an indication by the Examiner of allowable subject matter.

CONCLUSION

Claims 61-67 and 69-76 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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